

# A phase II study of the combination of docetaxel and bevacizumab for previously treated non-small cell lung cancer

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Tetsuo Shimizu , Yoshiko Nakagawa,  
Yasuo Asai, Ichirou Tsujino, Noriaki Takahashi  
and Yasuhiro Gon

## Abstract

**Objective:** The standard therapies for previously treated advanced non-small cell lung cancer (NSCLC) include docetaxel (DOC). Bevacizumab (BV), an antivascular endothelial growth factor (VEGF) antibody, increases the antitumor effect of cytotoxic anticancer agents. A BV-containing combination regimen is recommended as the primary therapy for advanced non-squamous NSCLC. However, the efficacy of DOC + BV is unknown in patients with previously treated advanced NSCLC. We conducted a phase II clinical study of DOC + BV for patients with previously treated advanced non-squamous NSCLC.

**Methods:** Twenty-three patients were enrolled in this study from June 2011 through May 2014. Chemotherapy was repeated every 21 days unless there was evidence of disease progression or intolerance to the study treatment. We assessed efficacy and toxicity.

**Results:** The median progression-free survival was 30.7 weeks. The response rate was 47.8%. The most common grade  $\geq 3$  adverse events were neutropenia (20 patients, 87.0%) and febrile neutropenia (7 patients, 30.4%).

**Conclusions:** The combination of DOC and BV often resulted in serious neutropenia, suggesting that this regimen is difficult to tolerate.

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Division of Respiratory Medicine, Department of Internal  
Medicine, Nihon University School of Medicine,  
Tokyo, Japan

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## Corresponding author:

Tetsuo Shimizu, Division of Respiratory Medicine,  
Department of Internal Medicine, Nihon University  
School of Medicine, 30-1, Oyaguchi-Kamichou, Itabashi-  
ku, Tokyo, Japan, 173-8610.  
Email: [shimizu.tetsuo@nihon-u.ac.jp](mailto:shimizu.tetsuo@nihon-u.ac.jp)



**Keywords**

Docetaxel, bevacizumab, advanced non-squamous non-small cell lung cancer, adverse events, chemotherapy, disease recurrence

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**Introduction**

Each year, more than 1 million patients worldwide are diagnosed with lung cancer. Non-squamous non-small cell lung cancer (NSCLC), predominately adenocarcinoma, accounts for approximately 60% of all lung cancers. Patients with advanced non-squamous NSCLC usually receive a platinum-doublet regimen as first-line chemotherapy. The median overall survival (OS) is approximately 12 months, and satisfactory therapeutic efficacy has not been achieved. Furthermore, most patients with lung cancer require second-line chemotherapy after first-line chemotherapy because the median progression-free survival (PFS) is 5 months or shorter. Standard regimens include docetaxel (DOC)<sup>1,2</sup> and pemetrexed (PMT)<sup>3,4</sup> monotherapy for patients with advanced non-squamous NSCLC as second-line chemotherapy. In a phase III study, the response rates (RRs) for DOC and PMT monotherapy were 8.8% and 9.1%, respectively, the PFS times were 2.9 and 2.9 months, respectively, and the OS times were 7.0 and 8.3 months, respectively.<sup>5,6</sup> The prognosis of patients with previously treated advanced non-squamous NSCLC is poor.

Bevacizumab, a humanized monoclonal antibody against vascular endothelial growth factor (VEGF), can prevent the development of new blood vessels and inhibit tumor growth. Furthermore, it increases drug delivery to the tumor and decreases interstitial pressure within the tumor.<sup>7,8</sup> In a phase III study (Eastern

Cooperative Oncology Group [ECOG] 4599 study) of chemotherapy-naive patients with advanced NSCLC, treatment with bevacizumab plus paclitaxel and carboplatin significantly improved OS.<sup>9</sup> Bevacizumab plus platinum-based chemotherapy is the standard first-line chemotherapy regimen for advanced NSCLC.<sup>10–13</sup> Furthermore, prolongation of PFS using bevacizumab combination therapy has been reported for previously treated advanced NSCLC, and we believe that the combination of chemotherapy and bevacizumab is useful.<sup>14</sup> However, clinical studies of combination regimens containing bevacizumab for patients with previously treated advanced NSCLC have rarely been reported. The efficacy and tolerability of bevacizumab as second-line chemotherapy are unknown. We conducted a phase II study of DOC in combination with bevacizumab for the treatment of patients with previously treated advanced non-squamous NSCLC.

**Patients and methods****Patients**

Twenty-three patients with histologic or cytologic evidence of stage IIIB or IV non-squamous NSCLC who experienced disease recurrence after one prior systemic chemotherapy regimen were enrolled at Nihon University Itabashi Hospital (Tokyo, Japan) from June 2011 through May 2014. The eligibility criteria included

an age of at least 18 years and an ECOG performance status (PS) of 0–2. Patients who had previously received DOC were not eligible, but those who had previously received bevacizumab were eligible because resistance to this drug is rare. Major organ functions were examined 2 weeks before registration using the following requirements: neutrophil count  $> 1500/\mu\text{L}$ , hemoglobin  $> 9\text{ g/dL}$ , platelets  $> 75,000/\mu\text{L}$ , total bilirubin  $< 1.5$ -fold the upper normal limit, AST and ALT  $< 2.5$ -fold the upper normal limit, serum creatinine  $< 1.2\text{ mg/dL}$ , serum albumin  $< 2.5\text{ g/dL}$ , and urinary protein  $< +1$ . The exclusion criteria were the presence of symptomatic brain metastases, hemoptysis, lung cavities, and infiltration of large vessels. Patients receiving anticoagulants were also excluded. This study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the clinical research judging committee of Nihon University Itabashi Hospital. Written informed consent was obtained from all patients.

### *Study design and treatment*

This study was an open-label phase II trial. The primary endpoint was PFS. Secondary endpoints were the response rate (RR), disease control rate (DCR), OS, and adverse events (AEs). Tumor response was assessed using the Response Evaluation Criteria in Solid Tumors. AEs were assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

Patients received DOC ( $60\text{ mg/m}^2$ ) infused intravenously for 60 minutes and bevacizumab ( $15\text{ mg/kg}$ ) infused intravenously for 30 minutes on day 1, in line with the approved doses of DOC and bevacizumab in Japan. Chemotherapy was repeated every 21 days unless there was evidence of disease progression or intolerance to the study treatment. Investigators were

required to confirm efficacy in this study for 2 years.

### *Statistical analysis*

A sample size of 30 patients was estimated on the basis of the projected median PFS of 3.4 months and on the basis of the log-rank test with an alpha level of 5% (two-sided) and a power of 80%.<sup>14</sup>

PFS was defined as the time from registration to the first date of disease progression or death of any cause. OS was defined as the time from registration to death of any cause. The time to response was defined as the duration from administration to the date of a confirmed complete or partial response. The distributions of PFS and OS were estimated using the Kaplan–Meier method. The chi-squared test was performed to compare patient characteristics (sex, histology, epidermal growth factor receptor [EGFR] mutation, prior regimens, smoking history, treatment course), RR, DCR, and AEs between the two groups. The log-rank test was performed using the Kaplan–Meier method to compare PFS and OS between the two groups.  $p < 0.05$  indicated a statistically significant difference. The analysis was performed using StatView 5.0 (SAS, Cary, NC).

## **Results**

### *Patient characteristics*

Patient characteristics are listed in Table 1. The median patient age was 62.1 years (range, 40–72 years). The most common patient characteristics were male sex, current or former smoker, prior history of adenocarcinoma, ECOG PS of 1, presence of stage IV cancer, and receipt of one prior regimen. No patients were EGFR mutation-positive. The mean number of treatment cycles was 8.4 (range, 1–28 cycles). In total, 43% of patients had

previously received radiation. In addition, 100%, 57%, 22%, and 30% of patients had previously received platinum-based chemotherapy, PMT, paclitaxel, and bevacizumab, respectively.

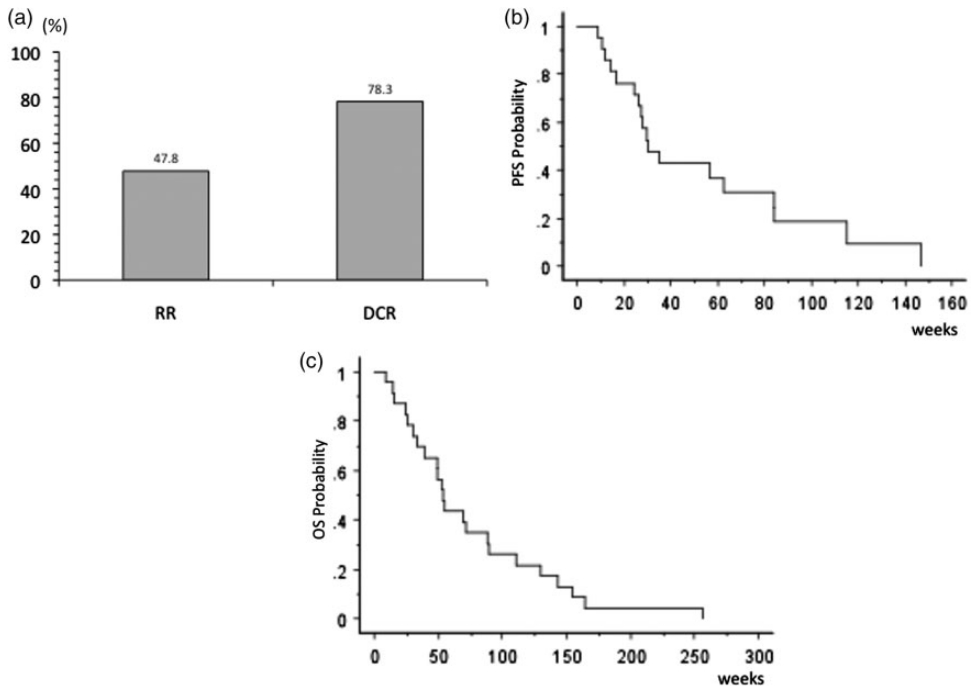
**Table 1.** Patient characteristics.

Number of patients	23
Mean age, years (range)	62.1 (40–72)
Sex (male/female)	16/7
Histology	
Adenocarcinoma	20
Non-small cell carcinoma	2
Large cell carcinoma	1
EGFR mutation-positive	0
Prior regimens	
1	19
2	3
3 or more	1
Never-smokers	4
Mean number of courses (range)	8.4 (1–28)

## Efficacy

The RR and DCR were 47.8% and 78.3%, respectively. The rate of progressive disease was 21.7%. The median PFS was 30.7 weeks (95% confidence interval [CI]= 25.8–57.3 weeks). The median OS was 88.3 weeks (95% CI= 42.9–100.1 weeks) (Figure 1).

Patients were divided by age (<65 years, non-elderly group;  $\geq$ 65 years, elderly group) to determine its potential effects on efficacy. The characteristics of these groups are shown in Table 2. Sex, PS, and the number of prior regimens were not significantly different between the two groups. In the non-elderly group, the RR, DCR, median PFS, and median OS were 45.5%, 72.7%, 27.4 weeks, and 49.6 weeks, respectively, compared with 50%, 83.3%, 62.9 weeks, and 89.1 weeks,



**Figure 1.** (a) Response rate (RR) and disease control rate (DCR), Kaplan–Meier (b) progression-free survival (PFS) curve, and (c) overall survival (OS) curve for patients with advanced non-squamous non-small cell lung cancer (NSCLC) who were treated with docetaxel (DOC) plus bevacizumab (BV).

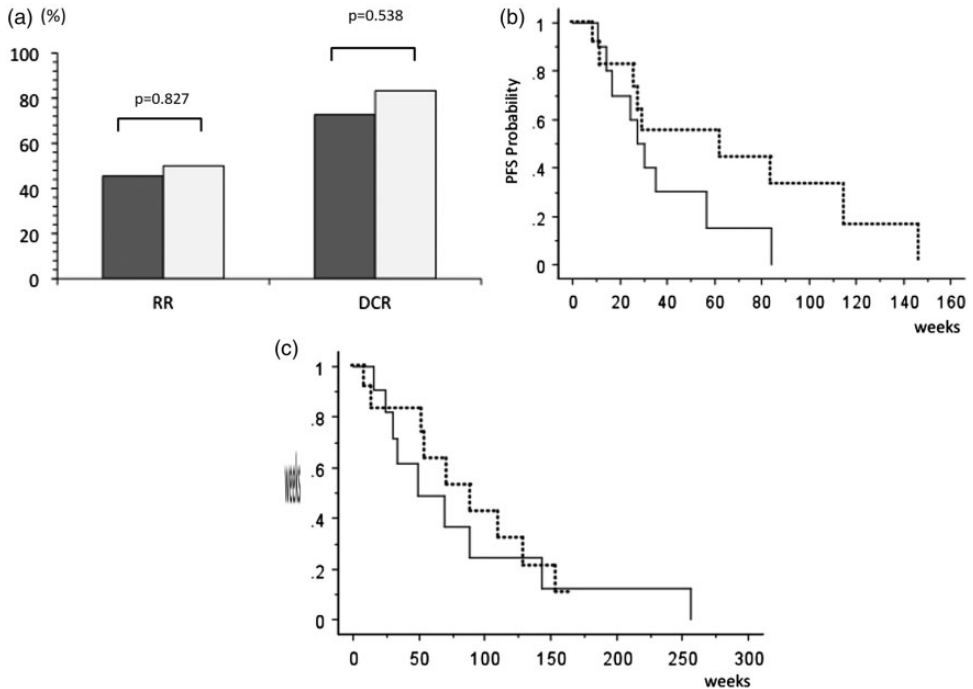
**Table 2.** Patient characteristics (non-elderly versus elderly patients).

	Non-elderly	Elderly
Number of patients	11	12
Mean age, years (range)	53.7 (40–62)	67.6 (65–72)
Sex (male/female)	7/4	9/3
Histology		
Adenocarcinoma	11	9
Non-small cell carcinoma	0	2
Large cell carcinoma	0	1
EGFR mutation-positive	0	0
Number of prior regimens		
1	9	10
2	2	1
3 or more	0	1
Never-smokers	3	1
Mean number of courses (range)	7.5 (2–22)	9.3 (1–28)

respectively, in the elderly group. These differences were not statistically significant (Figure 2).

**Time to response**

Eleven patients had a complete or partial response. Patients were assigned to two groups based on response. Specifically, the response group included patients with a complete or partial response, and the non-response group included patients with stable or progressive disease. Patient characteristics were not significantly different between the response and non-response groups (data not shown). The median time to response was 49 days (8–101 days).



**Figure 2.** (a) Response rate (RR) and disease control rate (DCR) in the non-elderly (black bar) and elderly groups (white bar) of patients with advanced non-squamous non-small cell lung cancer (NSCLC) who were treated with docetaxel (DOC) plus bevacizumab (BV) patients treated with DOC plus BV. Kaplan–Meier (b) progression-free survival (PFS) and (c) overall survival (OS) curves of the non-elderly and elderly groups. The dotted line denotes the elderly group, and the straight line denotes the non-elderly group.

**Table 3.** Summary of adverse events.a) All-grade adverse events vs. grade  $\geq 3$  adverse events

	All grade (%)	Grade $\geq 3$ (%)
Hematologic adverse events		
Neutropenia	87.0	65.2
Febrile neutropenia	30.4	21.7
Anemia	87.0	4.3
Thrombocytopenia	21.7	0
Non-hematologic adverse events		
Nausea	30.4	4.3
Rash	26.1	8.7
Hemorrhage	13.0	4.3
Proteinuria	47.8	0

b) Grade  $\geq 3$  adverse events (non-elderly versus elderly patients)

	Non-elderly (%)	Elderly (%)
Hematologic adverse events		
Neutropenia	54.5	75.0
Febrile neutropenia	18.3	25.0
Anemia	9.1	0
Thrombocytopenia	0	0
Non-hematologic adverse events		
Nausea	0	8.3
Rash	9.1	8.3
Hemorrhage	0	8.3
Proteinuria	0	0

**Post-treatment**

Eleven patients (47.8%) were able to receive chemotherapy, and the others were given best supportive care after this study. The most common chemotherapies were PMT (4 patients) and S-1 (4 patients). The most frequent causes of the change in treatment were progressive disease (15 patients, 65.2%) and AEs (7 patients, 30.4%).

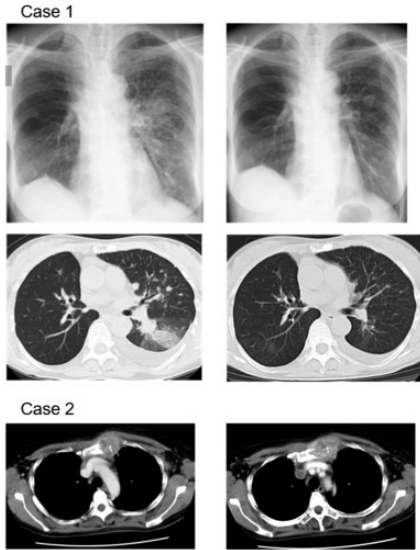
**AEs (Table 3)**

Most toxicities were hematologic. The most common AEs were neutropenia, anemia, and proteinuria. The most common grade  $\geq 3$  AEs were neutropenia (20 patients, 87.0%) and febrile neutropenia (7 patients, 30.4%). The incidence of anemia was high, but serious

anemia was rare. Patients in the elderly group experienced a higher incidence of grade  $\geq 3$  AEs (neutropenia and febrile neutropenia) than those in the non-elderly group.

**Cases**

The cases of two patients (a responder and a patient with AEs) are shown in Figure 3. The first patient (case 1) was a 67-year-old woman who had been diagnosed with EGFR mutation-negative adenocarcinoma of the lungs. Chest X-ray during pre-treatment revealed a tumor shadow in the left lower lobe. DOC and bevacizumab were given as second-line chemotherapy, which effectively reduced the size of the tumor. A partial response was achieved



**Figure 3.** Case 1: A 67-year-old woman with EGFR mutation-negative adenocarcinoma. The left panel shows chest X-ray and computed tomography (CT) scans obtained upon admission. The chest X-ray and CT scans after the administration of docetaxel plus bevacizumab (right panel) reveal a reduction in tumor size (partial response).

Case 2: A 53-year-old woman with EGFR mutation-negative adenocarcinoma. The left panel shows a chest computed tomography (CT) scan obtained upon admission. A chest CT scan after the administration of docetaxel plus bevacizumab (right panel) reveals a massive thrombus in the right internal jugular vein.

after only one course of therapy. The time to response was 45 days. The second patient (case 2) was a 53-year-old woman who had been diagnosed with EGFR mutation-negative adenocarcinoma of the lungs. DOC and bevacizumab were given as second-line chemotherapy. After 15 days of administration, chest computed tomography (CT) revealed a massive thrombus in the right internal jugular vein. Anticoagulation therapy consisting of heparin and warfarin was immediately administered, and chest CT revealed a reduced thrombus. Chemotherapy consisting of

DOC and bevacizumab was discontinued because of grade  $\geq 3$  thrombus.

## Discussion

When this study was designed, the standard therapy for previously treated advanced non-squamous NSCLC was DOC or PMT monotherapy. In a phase III study of DOC or PMT monotherapy, the PFS was 10.6 weeks or 2.9 months. In this study, the dose of docetaxel was set as  $60 \text{ mg/m}^2$ , which is the approved dose in Japan.<sup>15</sup> This dose is lower than that used in a phase III study of DOC monotherapy ( $100 \text{ mg/m}^2$ ). PFS was longer in our study than in the aforementioned phase III study of DOC or PMT monotherapy. Yamaguchi et al.<sup>16</sup> reported a phase II study examining the combination of DOC with bevacizumab in patients with previously treated NSCLC. The PFS of their study was shorter than that of our study because many patients received the treatment in the second-line setting in our study. We consider DOC plus bevacizumab an effective regimen for treating NSCLC.

Bevacizumab decreases interstitial pressure in the tumor microenvironment and increases drug delivery to the tumor. As a result, bevacizumab increases the efficacy of cytotoxic chemotherapy compared with that of chemotherapy alone. In this study, the RR and DCR were higher than those reported in a phase III study of DOC monotherapy. We believe that the RR and DCR were improved because of the addition of bevacizumab. In a phase II study of carboplatin plus paclitaxel with bevacizumab, the time to response was shorter in patients who also received bevacizumab than in those who did not receive the drug.<sup>13</sup> In this study, the time to response was 49 days. Most patients responded after only one or two courses of therapy.

Regarding AEs in this study, the incidence of grade 3 or greater neutropenia



was high, with 87.0% of patients developing neutropenia and 30.4% developing febrile neutropenia. Prophylaxis with granulocyte colony-stimulating factor (G-CSF) was not performed in this study, and remedial administration of G-CSF was required in many cases. Severe neutropenia was reported in another clinical trial of the DOC + bevacizumab combination.<sup>17</sup> When using this regimen, we believe that prophylaxis with a sustained G-CSF preparation is necessary. Additionally, serious thrombosis developed in non-hemotoxic patients, and it appeared that high chemotherapy doses were linked to the development of thrombosis. Best supportive care was most commonly used during the post-treatment period (52.2% of patients). Side effects such as neutropenia were substantial, and the PS decreased with toxicity. Other than progressive disease, AEs caused changes in treatment in 30.4% of patients. For this regimen, AEs influenced the continuation of treatment.

We explored whether the onset of treatment effects and AEs varied according to patient age. Differences in patient age did not cause the observed effects. Concerning AEs, many elderly patients developed grade 3 or greater neutropenia and febrile neutropenia. We are not able to recommend this regimen for elderly people because of the AE.

We regard DOC + bevacizumab as a promising regimen for patients with previously treated non-squamous NSCLC, especially after the failure of immune checkpoint inhibitors. We believe that many patients who develop neutropenia and febrile neutropenia may have difficulty tolerating the regimen. This finding suggests that a reduction in the dose of DOC and prophylaxis with a sustained-duration form of G-CSF are necessary.

#### Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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#### ORCID iD

Tetsuo Shimizu  <https://orcid.org/0000-0003-3405-9652>

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